ORIGINAL ARTICLE

Different Methods of Low-density Lipoprotein Cholesterol Estimation and the Impact on Lipid-lowering Therapy in Patients with Coronary Artery Disease

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Abstract

Background: Indirect estimation of low-density lipoprotein cholesterol (LDL-C) is a common clinical practice. The Friedewald equation is used most often but has inherent limitations. Clinical implications of such a practice have not been well defined, especially in the current era of targeting low (<50–70 mg/dL) or ultralow (<30–40 mg/dL) LDL-C levels.

Methods: Overall, 3,028 consecutive subjects with coronary artery disease (CAD) undergoing coronary revascularization were included. Four methods of LDL-C estimation were compared: direct estimation, the Friedewald, Martin, and Sampson equations.

Results: The mean age of the subjects was 61.3 ± 10.2 years, and 2,525 (83.4%) were men. Mean direct LDL-C was 78.9 ± 32.9 mg/dL. Compared with the direct estimation, all three indirect methods significantly underestimated LDL-C, but the Martin equation had the least bias (mean differences of −10.5 ± 9.7 mg/dL, −5.2 ± 7.6 mg/dL, and −7.2 ± 8.3 mg/dL with the Friedewald, Martin, and Sampson equations, respectively; *p*-values <0.001 for all the comparisons). Among patients with LDL-C >70 mg/dL and >50 mg/dL, the Friedewald equation erroneously classified 24.6% and 19.9%, respectively, as having LDL-C below these thresholds. This error increased with increasing triglyceride levels. The Martin equation was the most accurate, whereas the Sampson equation had intermediate accuracy.

Conclusion: Our study shows that the Friedewald equation underestimates LDL-C and can potentially result in significant undertreatment in patients with CAD in whom aggressive LDL-C lowering is crucial. Direct estimation is the preferred method, but the Martin equation could be a reasonable alternative if the direct estimation is not feasible due to logistical constraints.

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Introduction

Dyslipidemia is among the most important risk factors for atherosclerotic cardiovascular disease (ASCVD). Low-density lipoprotein cholesterol (LDL-C) is the main culprit and hence, the primary target for therapy.[1] A meta-analysis of several randomized trials has shown that for every 1 mmol/L reduction in LDL-C, there is an approximately 21% relative reduction in the risk of ASCVD events.[2] The patients with the highest baseline ASCVD risk benefit the most. Accordingly, all guidelines recommend aggressive LDL-C lowering to <50–70 mg/dL in patients with established ASCVD and to even lower levels (<30–40 mg/dL) in those with recurrent vascular events, polyvascular disease, or other high-risk features.[3–5]

Accurate estimation of LDL-C is crucial for properly guiding lipid-lowering therapy, especially in patients in whom aggressive LDL-C reduction is required. Direct estimation using enzymatic assays is considered the most accurate method. However, due to cost constraints and other logistical issues, many laboratories worldwide, and especially in India, continue to estimate LDL-C using indirect methods. The Friedewald equation[6] is the most commonly used method for this purpose, but it has inherent limitations. To overcome these limitations, many different equations have been proposed, which have variable accuracy.[7,8] Of all these methods, the Martin equation[9] and the Sampson equation[10] appear to be the most accurate.[7,8,11] Newer machine learning methods are also being explored, but the data are limited at present.[12,13]

Although several studies have compared the accuracy of the different methods of LDL-C estimation,[7,8,11,14] only a few have evaluated the potential impact of the measurement error on the therapeutic decision-making.[15–17] Hence, we sought this study to assess the potential impact of indirect LDL-C estimation on the lipid-lowering therapy in patients with established coronary artery disease (CAD) in whom this issue would be of the greatest relevance. We selected the three clinically most relevant, indirect methods of LDL-C estimation—the Friedewald equation, Martin equation, and Sampson equation.

Methods

This was a retrospective study conducted at a premier, tertiary care center in North India. All subjects with newly diagnosed CAD who had undergone coronary revascularization at our center during the period 1 January 2023 to 31 December 2023 were included. The patients in whom a lipid profile was not done during the index hospitalization were excluded. If a patient had had multiple coronary interventions during this 1-year period, only the first hospitalization was considered. Based on these criteria, 3,064 subjects were found to be eligible for inclusion in this study. Of these, 36 subjects (1.2% of all) with serum triglycerides (TG) >400 mg/dL were also excluded because both the Friedewald and the Martin equations are not applicable if TG is above 400 mg/dL.

For all subjects, baseline lipid profile findings, along with relevant clinical and biochemical details, were retrieved from the hospital medical records. As per the hospital policy, all patients had undergone fasting lipid profile estimation within the first 24 hours of their presentation. Enzymatic assays on the Vitros Dry Chemistry Autoanalyzer were used for measuring total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and TG. The LDL-C estimation was done using the two-step cholesterol esterase/

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cholesterol oxidase/peroxidase and catalase method. LDL-C was also estimated indirectly using the following three methods:

- *Friedewald equation*:[6] LDL-C = TC–HDL-C–TG/5 (all values in mg/dL)
- *Martin equation*: The Martin equation is almost identical to the Friedewald equation, except that the fixed factor '5' is replaced with an adjustable factor. This adjustable factor is derived from a 180-cell table that takes into consideration the patient's TG and non-HDL-C.[9] Batch calculation of LDL-C can be performed using an Excel spreadsheet, which can be downloaded from www.ldlcalculator.com. We used the 5,000-row version of the spreadsheet to match our sample size.
- *Sampson equation*: The following equation was used[10] [LDL-C = TC/0.948−HDL-C/0.971−(TG/8.56+TG×Non-HDL-C/2140−TG^2/16100)−9.44]

For all the above methods, the proportions of the patients having LDL-C <70 mg/dL and <50 mg/dL were calculated. This calculation was done for the entire study population as well as for the groups based on TG levels, as follows:

- 0–99 mg/dL,
- 100–199 mg/dL,
- 200–299 mg/dL, and
- 300–399 mg/dL

We also calculated non-HDL-C by subtracting HDL-C from TC.

The study was approved by the Institutional Review Board and the Independent Ethics Committee [MICR 1722/2024 (academic)]. The requirement for patient consent was waived because of the retrospective nature of the study.

Statistical Analysis

The baseline characteristics and other descriptive variables were summarized using standard statistical tools such as mean ± standard deviation or counts and proportions as appropriate. The repeated measures analysis of variance with the Bonferroni method for *post hoc* comparison was used for comparing the LDL-C values derived using the different methods. The correlations among the different LDL-C values were assessed using Pearson's correlation coefficients, and Fisher's *z*-transformation was used for comparing the strengths of different correlations (https://www.psychometrica.de/correlation.html). A two-sided *p*-value <0.05 was considered statistically significant. All the analyses were performed using SPSS version 20.0.

Results

A total of 3,028 subjects were included in this study. The mean age of the study subjects was 61.3 ± 10.2 years, and 2,525 (83.4%) were men.

Baseline Characteristics

Table 1 summarizes clinical and laboratory characteristics of the study subjects. Diabetes mellitus was present in 1,583 (52.5%) subjects, and hypertension in 1,901 (62.8%). Acute coronary syndrome was the presentation in 1,185 (39.1%) subjects, and the majority (1,838; 60.7%) had undergone percutaneous coronary intervention.

Table 2 summarizes the lipid parameters in the study population. The mean LDL-C using the direct method was 78.9 ± 32.9 mg/dL. Low HDL-C was present in 71.6% patients. Mean TG was 144.4 ± 57.8 mg/dL, with the vast majority (85.7%) having TG <200 mg/dL.

Low-density Lipoprotein Cholesterol Using the Different Methods

Compared with the direct method, all three indirect methods significantly underestimated the LDL-C (Table 3). The Friedewald equation provided the lowest values, whereas the Martin equation had the least negative bias. Despite this systematic underestimation, there was a significant correlation among the different methods for LDL-C estimation. However, the Martin equation had the strongest correlation with direct LDL-C as compared to the other two indirect methods (Table 4).

Attainment of the Low-density Lipoprotein Cholesterol Goals

The direct LDL-C was >70 mg/dL in 1,616 (53.4%) subjects (Table 5). The Friedewald equation categorized 24.6% of these as having LDL-C <70 mg/dL (Fig. 1). This error increased with increasing TG levels (p <

Table 1: Clinical and laboratory characteristics of the study population

Parameter	*Overall (n = 3,028)*
Age, years	61.3 ± 10.2
Male gender	2,525 (83.4)
Hypertension	1,901 (62.8)
Diabetes mellitus	1,583 (52.3)
Hypothyroidism	311 (10.3)
Systolic blood pressure, mm Hg	129 ± 15
Diastolic blood pressure, mm Hg	78 ± 9
Hemoglobin, g/dL	13.0 ± 1.7
Glycosylated hemoglobin, %	7.0 ± 1.7
Blood urea, mg/dL	41.3 ± 23.2
Serum creatinine, mg/dL	1.1 ± 0.7
Serum uric acid, mg/dL	6.1 ± 1.8
Acute coronary syndrome	1,185 (39.1)
Procedure	
Percutaneous coronary angioplasty	1,838 (60.7)
Coronary artery bypass surgery	1,190 (39.3)

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses

Table 2: Lipid parameters in the study population

Parameter	*Overall (n = 3,064)*
Total cholesterol, mg/dL	134.0 ± 40.1
Direct LDL-C, mg/dL	78.9 ± 32.9
HDL-C, mg/dL	36.7 ± 10.0
Low HDL-C (<40 in men, <50 in women)	2,167 (71.6)
Triglycerides, mg/dL	144.4 ± 57.8
0–99 mg/dL	636 (21.0)
100–199 mg/dL	1,959 (64.7)
200–299 mg/dL	357 (11.8)
300–399 mg/dL	76 (2.5)
Non-HDL-C, mg/dL	97.2 ± 37.8

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

Table 3: Low-density lipoprotein cholesterol estimated using different methods

Parameter	*n = 3,028*
Direct measurement, mg/dL	78.9 ± 32.9
Friedewald equation	
LDL-C, mg/dL	68.3 ± 34.4
Difference, mg/dL	−10.5 ± 9.7
Martin equation	
LDL-C, mg/dL	73.6 ± 34.0
Difference, mg/dL	−5.2 ± 7.6
Sampson equation	
LDL-C, mg/dL	71.6 ± 34.4
Difference, mg/dL	−7.2 ± 8.3

All values are reported as mean ± standard deviation. The LDL-C values derived using all four methods differed significantly from each other, with a *p*-value <0.001; LDL-C, low-density lipoprotein cholesterol

0.001). The corresponding proportions were much lower for the Martin and the Sampson equations, with the Martin equation being the most accurate. Neither of these equations was affected by the TG category ($p > 0.05$).

Similar findings were seen in patients with direct LDL-C >50 mg/dL (Table 5). However, for this group, the accuracy of the Martin equation improved with increasing TG levels.

A significantly higher proportion of males achieved the LDL-C goals (both <50 mg/dL and <70 mg/dL) as compared to females, regardless of the measurement method (Table 6).

Table 4: Correlation among different methods for low-density lipoprotein cholesterol estimation (*n* = 3,028)

	Pearson's correlation coefficients			
	Direct measurement	*Friedewald equation*	*Martin equation*	*Sampson equation*
Direct measurement	1	0.959*	0.975*	0.971*
Friedewald equation	0.959	1	0.986	0.996
Martin equation	0.975	0.986	1	0.997
Sampson equation	0.971	0.996	0.997	1

All correlations had *p*-values <0.001; *The Martin equation had a much stronger correlation with the direct measurement as compared to the other two indirect methods (*p*-value 0.017 for comparison with the Sampson equation and <0.001 for comparison with Friedewald equation)

Table 5: Attainment of low-density lipoprotein cholesterol goals according to the different estimation methods and the serum triglycerides categories

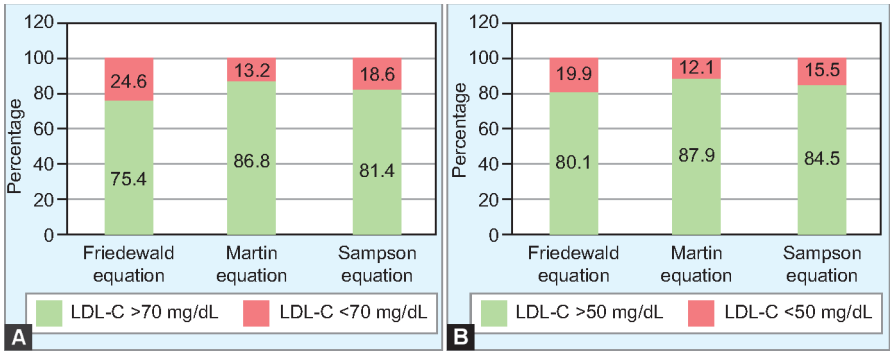
Direct LDL-C >70 mg/dL (n = 1,616, 53.4% of all)						
TG category ↓	*Friedewald equation*		*Martin equation*		*Sampson equation*	
	<70 mg/dL	*>70 mg/dL*	*<70 mg/dL*	*>70 mg/dL*	*<70 mg/dL*	*>70 mg/dL*
Overall	398 (24.6)	1,218 (75.4)	214 (13.2)	1,402 (86.8)	300 (18.6)	1,316 (81.4)
0–99 mg/dL (*n* = 216)	34 (15.7)	182 (84.3)	34 (15.7)	182 (84.3)	33 (15.3)	183 (84.7)
100–199 mg/dL (*n* = 1078)	263 (24.4)	815 (75.6)	144 (13.4)	934 (86.6)	200 (18.6)	878 (81.4)
200–299 mg/dL (*n* = 260)	77 (29.6)	183 (70.4)	32 (12.3)	228 (87.7)	53 (20.6)	207 (79.6)
300–399 mg/dL (*n* = 62)	24 (38.7)	38 (61.3)	4 (6.5)	58 (93.5)	14 (22.6)	48 (77.4)
p-value for the trend	<0.001		0.276		0.428	
Direct LDL-C >50 mg/dL (n = 2,512, 83.0% of all)						
TG category ↓	*Friedewald equation*		*Martin equation*		*Sampson equation*	
	<50 mg/dL	*>50 mg/dL*	*<50 mg/dL*	*>50 mg/dL*	*<50 mg/dL*	*>50 mg/dL*
Overall	500 (19.9)	2,012 (80.1)	304 (12.1)	2,208 (87.9)	389 (15.5)	2,123 (84.5)
0–99 mg/dL (*n* = 450)	69 (15.3)	381 (84.7)	76 (16.9)	374 (83.1)	74 (16.4)	376 (83.6)
100–199 mg/dL (*n* = 1656)	334 (20.2)	1322 (79.8)	199 (12.0)	1,457 (88.0)	251 (15.2)	1,405 (84.8)
200–299 mg/dL (*n* = 335)	79 (23.6)	256 (76.4)	26 (7.8)	309 (92.2)	54 (16.1)	281 (83.9)
300–399 mg/dL (*n* = 71)	18 (25.4)	53 (74.6)	3 (4.2)	68 (95.8)	10 (14.1)	61 (85.9)
p-value for the trend	0.017		<0.001		0.882	

All values are actual numbers with percentages in parentheses; LDL-C, low-density lipoprotein cholesterol; TG, serum triglycerides

Table 6: Attainment of low-density lipoprotein cholesterol goals in males and females according to the different estimation methods

	LDL-C <50 mg/dL				*LDL-C <70 mg/dL*			
	Overall (n = 3,028)	*Males (n = 2,525)*	*Females (n = 503)*	*p-value*	*Overall (n = 3,028)*	*Males (n = 2,525)*	*Females (n = 503)*	*p-value*
Direct method	516 (17.0)	442 (17.5)	74 (14.7)	0.128	1,412 (46.6)	1,219 (48.3)	193 (38.4)	<0.001
Friedewald equation	1003 (33.1)	877 (34.7)	126 (25.0)	<0.001	1789 (59.1)	1527 (60.5)	262 (52.1)	<0.001
Martin equation	796 (26.3)	699 (27.7)	97 (19.3)	<0.001	1585 (52.3)	1369 (54.2)	216 (42.9)	<0.001
Sampson equation	887 (29.3)	779 (30.9)	108 (21.5)	<0.001	1683 (55.6)	1442 (57.1)	241 (47.9)	<0.001

All values are actual numbers with percentages in parentheses; LDL-C, low-density lipoprotein cholesterol



Figs 1A and B: Categorization of the patients above or below the specific low-density lipoprotein cholesterol (LDL-C) thresholds according to the different methods for indirect LDL-C estimation. (A) Patients with direct LDL-C >70 mg/dL (*n* = 1,616). (B) The patients with direct LDL-C >50 mg/dL (*n* = 2,512)

Discussion

Ours is the first study to provide a direct perspective on the treatment implications of the LDL-C estimation methods in contemporary clinical practice. The study shows that in patients with CAD, indirect LDL-C estimation using the Friedewald equation can potentially lead to undertreatment in approximately 25% of the subjects if the LDL-C target is <70 mg/dL and in 20% subjects if the target is <50 mg/dL. This inaccuracy increases with increasing TG levels. The Martin equation and the Sampson equation provide a more accurate assessment, with the former being the most reliable.

Need for Aggressive Low-density Lipoprotein Cholesterol Reduction

Atherosclerotic cardiovascular disease is the leading killer in the world, accounting for more than 25% of all deaths.[18] The Indian population is worse affected with not only a higher prevalence of the disease, but also more premature onset and a higher case fatality rate.[19] Aggressive LDL-C lowering is one of the most effective strategies to reduce the mortality associated with ASCVD. The trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have shown that there is an incremental reduction in the ASCVD risk at ultralow LDL-C levels with no apparent threshold below which the benefit ceases to exist.[20,21] There are also no apparent safety concerns even at very low LDL-C levels.[22–24] Accordingly, all the leading societies recommend lowering LDL-C to at least <50–70 mg/dL in all patients with ASCVD.[3–5] Even lower targets (<30–40 mg/dL) have been recommended for patients with recurrent vascular events, polyvascular disease, and other high-risk features.[4,5]

Low-density Lipoprotein Cholesterol Estimation

Accurate LDL-C estimation is crucial for proper guidance of lipid-lowering therapy, especially in the current era of achieving very low LDL-C levels. The direct estimation of LDL-C using one of the enzymatic methods is considered the most accurate method for LDL-C estimation. However, due to the cost constraints and other logistical reasons, many laboratories worldwide continue to use indirect methods for estimating LDL-C. There are also issues with the standardization of the analytic methodology used for direct LDL-C estimation.

The Friedewald equation is the most popular method for indirect estimation. Proposed by Friedewald in 1972, the equation requires TC, HDL-C, and TG to estimate LDL-C.[6] This method is applicable only if TG is <400 mg/dL. Although this equation works well for day-to-day clinical needs, it has several limitations that are well recognized. First, the equation is not applicable if TG is >400 mg/dL. Second, the accuracy of this method is compromised as the TG increases above 150 mg/dL or when LDL-C is very low, the latter being very relevant to the current clinical practice. And third, a fasting blood sample is required for minimizing errors, which presents a major practical challenge as most of the current guidelines nowadays recommend non-fasting sampling for initial LDL-C estimation.[3–5]

Several different equations have been proposed to overcome various limitations inherent to the Friedewald equation.[7,8] More than 25 such equations are currently available, which have been compared in many different studies. These studies have shown inconsistent accuracy of these equations, which varies according to the population studied.[7,8,11,14] The two equations, however, appear to be the most robust–the Martin equation and the Sampson equation.[7,8,11,14] The former is applicable up to TG <400 mg/dL whereas the latter can be used even in patients with TG up to 800 mg/dL. The Martin equation has been shown to have very good accuracy even at very low LDL-C levels, as seen in the trials with the PCSK9 inhibitors.[25,26]

The accuracy of the Friedewald, Martin, and Sampson equations has been compared in several studies. Most of these studies have shown that all three equations lead to underestimation of LDL-C, but the Martin equation has the least bias.[7,8,11,14] Furthermore, whereas the error with the Friedewald equation increases with increasing TG levels, the accuracy of the Martin equation remains stable.[27] In our study, we also found exactly similar results.

Although numerous studies have tested the accuracy of various methods for LDL-C estimation, very few have evaluated the impact of the measurement error on treatment decisions, especially in patients with established ASCVD in whom achieving low/very low LDL-C is crucial.[15–17] Shi et al. studied 30,349 individuals with angiographically proven CAD. LDL-C was underestimated by all the three methods (Friedewald, Martin, and Sampson) in comparison to the direct estimation. The underestimation increased when TG was >150 mg/dL. Among patients with LDL-C 70–100 mg/dL, the three equations categorized 37.7, 19.2, and 26% of the subjects, respectively, as having LDL-C <70 mg/dL. The corresponding figures for patients with LDL-C 55–70 mg/dL, categorized as having LDL-C <55 mg/dL, were 53.6, 29, and 39.8%, respectively.[15] These findings are very similar to ours, except that the proportional underestimation was much larger in the study by Shi et al. because only the patients within a specific LDL-C category were used as the denominator and not all those above a certain LDL-C threshold. Another analysis by the same group involving patients in their percutaneous coronary intervention registry also reported similar findings.[16] Zafrir et al. also, in a study of 10,009 individuals undergoing coronary angiography, showed significant misclassification of individuals into lower LDL-C categories using the Friedewald equation compared with the Martin and Sampson equations. However, the direct LDL-C was not measured in this study.[14] Incorrect classification into lower LDL-C categories has been reported in a few other studies as well.[17]

These studies collectively show that indirect estimation of LDL-C has significant potential to lead to undertreatment of individuals. However, the impact of such underestimation on the long-term outcome has not been studied. This issue is relevant because in many of the large-scale trials, which form the basis for the current guidelines, the LDL-C was measured using the Friedewald equation and not the direct methods. Unfortunately, no randomized controlled study

comparing treatment strategies based on the different methods of LDL-estimation is feasible due to ethical reasons. However, a recent study has shown that the 10- or 20-year ASCVD prediction models incorporating LDL-C values of the Martin equation have superior predictive ability than the models based on the Friedewald or Sampson equation.[28] Furthermore, since there is clear evidence to show that reduction of LDL-C to lower levels is associated with a lower risk of ASCVD events, it can be safely concluded that leaving the patients at a higher LDL-C level will be deleterious.

The major lipid guidelines have acknowledged these issues. The 2018 American College of Cardiology/American Heart Association guidelines mention that the Friedewald method is inaccurate when LDL-C is <70 mg/dL and instead recommend using either direct method or the Martin equation (class IIa).[3] Similarly, the National Lipid Association in 2021 has advocated using the Martin equation instead of the Friedewald equation in patients with LDL-C <100 mg/dL or TG 150–400 mg/dL.[29] The 2019 European Society of Cardiology guidelines have also highlighted the concerns about the suboptimal accuracy of the Friedewald method at very low LDL-C levels or when TG is >177 mg/dL. However, no clear recommendation is made for an alternative option.[4]

Limitations

Our study had a few limitations that need to be discussed. First, being a single-center study, our findings may not be generalizable. However, we wish to emphasize that in our study, the mean TG was 144.4 ± 57.8 mg/dL, which was in the normal range. Hence, the error in the LDL estimation observed with the Friedewald equation in our study is likely to be an underestimation only. Second, due to the cross-sectional and retrospective nature of the study, the long-term impact of treatment guidance using the different LDL estimation methods on clinical outcomes could not be assessed. However, as already mentioned, a prospective trial to answer this question is not feasible due to ethical reasons.

Conclusion

In conclusion, our study shows that the Friedewald equation underestimates LDL-C and can potentially result in significant undertreatment in patients with CAD in whom aggressive LDL-C lowering is crucial. Direct estimation is the preferred method, but the Martin equation could be a reasonable alternative if the direct estimation is not feasible due to logistical constraints.

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